Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 5481–5485
Tetrahedron

Synthesis of methylenedioxy-bearing 1-aryl-3-carboxylisoquinolines using a modified Ritter reaction procedure

Yves L. Janin,[a,*] Didier Decaudin,[b] Claude Monneret[c] and Marie-France Poupon[d]

[a]*URA 2128 CNRS-Institut Pasteur, 28 rue du Dr. Roux, 75724 Paris cedex 15, France*
[b]*Service d'Hématologie, CNRS-Institut Curie, 26 rue d'Ulm, 75248 Paris cedex 05, France*
[c]*UMR 176 CNRS-Institut Curie, 26 rue d'Ulm, 75248 Paris cedex 05, France*
[d]*UMR 147 CNRS-Institut Curie, 26 rue d'Ulm, 75248 Paris cedex 05, France*

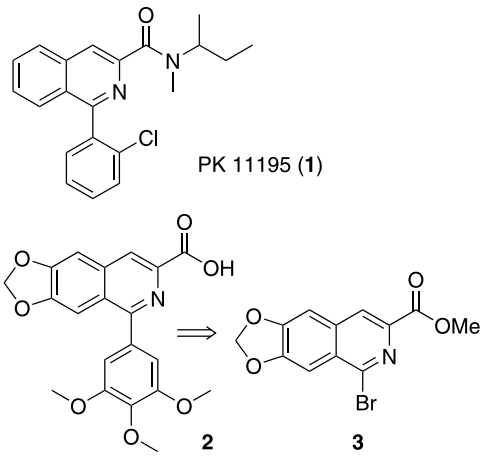
Received 12 January 2004; revised 1 April 2004; accepted 8 April 2004

Abstract—This paper describes original approaches aimed at the preparation of electron-rich 1-aryl-3-carboxylisoquinolines. Our first attempt led to an efficient preparation of 1-hydroxyisoquinoline-3-carboxylic acid methyl ester starting from bromophthalide via a rearrangement of 2-acetylamino-2-(3-oxo-1,3-dihydroisobenzofuran-1-yl)-malonic acid dimethyl ester. However, as its eventual application to the synthesis of methylenedioxy-bearing substrates seemed rather long, a second approach involving an extension of the Ritter reaction to safrole was devised. We thus report that, under proper experimental settings, the use of 54% tetrafluoroboric acid in ether enables a Ritter reaction between safrole and 3,4,5-trimethoxybenzonitrile yielding 17% of 7-methyl-5-(3,4,5-trimethoxyphenyl)-7,8-dihydro-[1,3]dioxolo[4,5-*g*]isoquinoline. This acidic reagent avoids the extensive decomposition seen when using the classical Ritter reaction conditions (i.e.: concentrated sulfuric acid). Further chemical transformations of this methyl-bearing dihydroisoquinoline led to the methylenedioxy-bearing 1-aryl-3-carboxylisoquinoline. These derivatives are related to the peripheral benzodiazepine receptor ligand PK 11195 as well as falcipain-2 inhibitors and other potential antitumor agents.

1. Introduction

In the course of our work[1,2] on the synthesis of potential peripheral benzodiazepine receptor ligands[3,4] related to the phenylisoquinoline PK 11195 (**1**), we undertook the preparation of the electron-rich analogue such as **2** which are incidentally related to falcipain-2 inhibitors[5] and compounds reported for their antitumor potential.[6–8]

The first approach to such electron-rich 1-aryl-3-carboxyl-isoquinolines we envisioned is based on the Suzuki palladium-catalysed aryl coupling reaction between aryl-boronate and 1-bromo-3-carboxylisoquinoline we previously described.[1] Thus a convergent approach from electron-rich isoquinolines such as compound **3** was planned (Scheme 1).

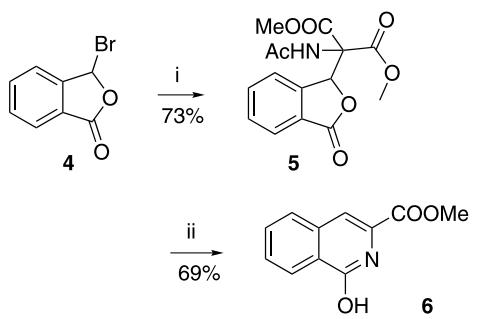


Scheme 1.

In the course of studies aimed at a simple preparation of compound **3**, we devised an original preparation of the 3-carboxyl isoquinolone **6** from bromophthalide (**4**) via lactone **5**. As depicted in Scheme 2, an alkylation of dimethyl acetamidomalonate to give lactone **5** efficiently provides a synthetic precursor bearing all the functional groups required. After various trials, we found that boiling lactone **5** in the presence of 1.1 equiv. of freshly distilled[9] boron trifluoride diethyl etherate complex in 1,2-dichloro-benzene for 30 min led to its decarboxylative rearrangement into the target isoquinolone **6** in a 69% yield.

Keywords: Ritter reaction; 1-Aryl-3-carboxylisoquinoline; PK11195.
* Corresponding author. Tel.: +33-1-45-68-83-95; fax: +33-1-45-68-84-04; e-mail address: yljanin@pasteur.fr

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.05.004



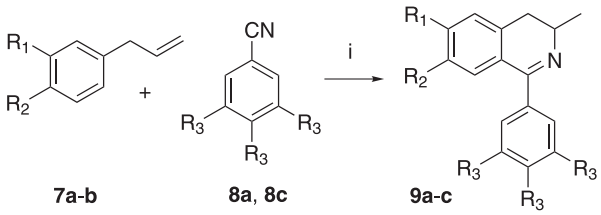
Scheme 2. (i) Dimethyl acetamidomalonate, NaH, DMF 25 °C. (ii) BF_3-OEt_2, 1,2-dichlorobenzene, 180 °C.

This method, with an overall 50% yield from commercially available material, is in fact a quite simple preparation of compound **6**.[1,10–15] However, although many bromophthalides have been described, the number of synthetic steps required to obtain target compound **2** via **3** remains important.

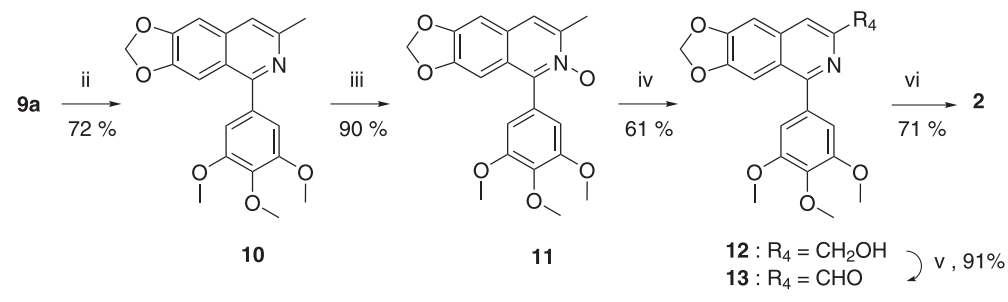
Thus we redirected our efforts to a second approach. What seems to be, in general, the quickest method to prepare the phenylisoquinoline system are the Bischler-Napieralsky reaction,[16,17] (from 2-phenylethyl benzamides) or the Pictet-Spengler reaction[18] (from 2-phenylethylamine and benzaldehyde), followed by aromatisation steps. The preparation of compound **10** has actually been reported using the Bischler-Napieralsky reaction.[19] However, if no yield is provided in that case, a more recent and remarkable work[6] reports excellent yield starting from electron-rich substrates (bearing relatively more stable 1,4-dioxane moieties). However, the fact that in our case, the synthesis of methylenedioxyphenylethylamine would have been uncomfortably close to research on the preparation of an illegal drug, we focused on a much less investigated approach based on the Ritter reaction[20,21] starting from safrole (**7a**). The initial report[22] describing the reaction between the electron-rich methyleugenol and veratronitrile mentions a 53% yield of the corresponding dihydroisoquinoline. However, the authors also state that no compound could be isolated when starting from safrole (**7a**). On the other hand, a contemporary research group described a low yield (6.5%) of an electron-rich 1-phenylisoquinoline which was obtained from safrole (**7a**) and veratricamide in boiling benzene in the presence of phosphorus oxychloride.[23] More remarkably, another group described the preparation of electron-rich 1-phenylisoquinoline from the vinylic isosafrole and piperonal oxime (or amide) under the same reaction conditions.[24,25]

Our first trials, starting from safrole (**7a**) and 3,4,5-trimethoxybenzonitrile (**8a**) in concentrated sulfuric acid, expectedly[22] only led to extensive decomposition. However, as early reports pointed out that a methylenedioxy group seems to tolerate relatively strong water-free acidic conditions,[19,23] we reasoned that the decomposition could be caused by the nature of the counter-ion of the acid used, and its water content. Accordingly, we tried other strong acids bearing a soft counter ion. Our best results were obtained with tetrafluoroboric acid in ether using a not very standard experimental setting (see Section 2). Thus a 17% yield of the isoquinoline **9a** was obtained using 1 equiv. of 3,4,5-trimethoxybenzonitrile (**8a**), 2 equiv. of safrole (**7a**) and tetrafluoroboric acid (Scheme 3). Trials with other substrates were undertaken and a yield of 36% of **9b** was obtained from methyleugenol (**7b**) and compound **8a**, whereas 16% of the corresponding dihydroisoquinoline **9c** was obtained from safrole (**7a**) and benzonitrile (**8c**). Moreover, less than 2% of dihydroisoquinoline was observed in a not quite pure chromatography fraction of the result of the reaction between allylbenzene and compound **8a**. These trials further confirmed the fragility of the safrole methylenedioxy moiety as well as the need for electron-donating groups on the allyl aryl component to obtain a cyclization reaction into dihydroisoquinoline.

From compound **9a**, an aromatisation step using palladium over charcoal gave compound **10**. This was followed by the 3-methyl oxidation[1] via the isoquinoline *N*-oxide **11** which produce compound **12** in a 61% yield. It is noteworthy that the use of acetic anhydride was necessary for the rearrangement of the *N*-oxide **11**, as the use of trifluoroacetic anhydride led to extensive acid-caused dealkylation and



	R_1	R_2	R_3	% **9**
a	OCH_2O		OCH_3	17%
b	OCH_3	OCH_3	OCH_3	36%
c	OCH_2O		H	16%



Scheme 3. (i) 54% HBF_4, Et_2O. (ii) Pd/C, decaline, reflux. (iii) 3-Chloroperoxybenzoic acid, CH_2Cl_2. (iv) (a) Ac_2O, 1,2-dichlorobenzene, reflux, (b) KOH, aqueous ethanol, 50 °C. (v) Dess–Martin periodinane, CH_2Cl_2. (vi) $AgNO_3$, NaOH, MeCN–H_2O.

subsequent decomposition. A two-stage oxidation of alcohol **12** via aldehyde **13** turned out to be necessary to obtain the target acid **2**, as no efficient method was found to oxidize directly alcohol **12** into acid **2**.

In conclusion, our first approach toward the preparation of the pentaoxygenated-1-aryl-3-carboxylisoquinoline **2** was based on a planned Suzuki reaction between 1-bromoisoquinoline **3** and arylboronates. Even if this led us to devise an original synthesis of 1-hydroxyisoquinoline-3-carboxylic acid methyl ester (**6**) an alternative to the inherently long preparations of oxygen-bearing bromophthalimides was sought. Thus a second approach, based on the Ritter reaction between safrole **7a** and 3,4,5-trimethoxybenzonitrile **8a**, was found possible by using tetrafluoroboric acid in ether under quite original reaction conditions (see Section 2). Although this synthesis provides, so far, a 17% yield of the dihydroisoquinoline **9a**, the very small number of steps following the quick preparation of this ring system provides a fast access to original electron-rich 1-arylisoquinolines bearing a functional group on carbon 3.

2. Experimental

2.1. General methods

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance-300 spectrometer at 300 and 75 MHz, respectively. Shifts (δ) are given in ppm with respect to the TMS signal and coupling constants (J) are given in Hertz. Column chromatography were performed on Merck silica gel 60 (0.035–0.070 mm). Low and high resolution mass spectra were obtained by Mrs Nicole Morin (ENS, 24 rue Lhomond, F-75231 Paris) on a MS 700 Jeol.

2.1.1. 2-Acetylamino-2-(3-oxo-1,3-dihydroisobenzofuran-1-yl)-malonic acid dimethyl ester (5). Dry dimethyl acetamidomalonate (6.51 g, 0.034 mol) was dissolved in dry DMF (260 mL; dried over 4 Å molecular sieves). To this solution was added 60% sodium hydride (suspension in mineral oil) (1.37 g, 0.034 mol). The suspension was stirred under a moisture-protected atmosphere (calcium chloride drying tube) for 30 min and then solid bromophthalide (**4**) (6.67 g, 0.031 mol) was added. The resulting mixture was stirred at room temperature overnight and then concentrated under a reduced pressure. The residue was dissolved in ethyl acetate (200 mL) and the suspension was washed with 1 N sodium hydroxide, water and dried over magnesium sulfate. After removal of the solvent, under reduced pressure, compound **5** was obtained as a solid (7.38 g, 73%) which could be used for the next step without further purification or recrystallized in a mixture of toluene and heptane, Mp 161 °C; ^{1}H NMR ($CDCl_3$) δ 7.97 (d, J=7.7 Hz, 1H), 7.78 (d, J=7.7 Hz, 1H), 7.60 (t, J=7.7 Hz, 1H), 7.49 (t, J=7.7 Hz, 1H), 6.55 (s (br), 1H), 6.31 (s, 1H), 3.92 (s, 3H), 3.73 (s, 3H), 1.69 (s, 3H); ^{13}C NMR ($CDCl_3$): δ=169.5, 168.8, 165.9, 165.6, 144.2, 133.5, 129.9, 127.4, 126.5, 124.4, 81.7, 67.6, 54.5, 53.3, 22.3. Anal. calcd for $C_{15}H_{15}NO_7$: C, 56.08; H, 4.71; N, 4.36; found C, 56.50; H, 4.72; N, 4.16.

2.1.2. 1-Hydroxyisoquinoline-3-carboxylic acid methyl ester (6). Compound **5** (1 g, 3.11 mmol) was dispersed in 1,2-dichlorobenzene (80 mL). The freshly distilled[9] boron trifluoride diethyl etherate complex (0.45 mL, 3.55 mmol) was added and the mixture was heated to reflux under a moisture-protected atmosphere (calcium chloride drying tube) for 30 min. The solution was allowed to cool, diluted in dichloromethane (100 mL), washed twice with water and dried over magnesium sulfate. After removal of the solvent under vacuum, the residue was purified by chromatography over silica gel eluting with a 99:1 mixture of dichloromethane and methanol to give compound **6** (0.44 g, 69%) which has characteristics identical with the previously reported data.[12]

2.1.3. 7-Methyl-5-(3,4,5-trimethoxyphenyl)-7,8-dihydro-[1,3]dioxolo[4,5-*g*]isoquinoline (9a). In a 2.5 L thick high density polyethylene bottle, safrole (**7a**) (10.07 g, 0.062 mol) and 3,4,5-trimethoxybenzonitrile (**8a**) (6 g, 0.031 mol) were mixed together at room temperature before 54% tetrafluoroboric acid in ether (10 mL, 0.072 mol) was added and the bottle quickly (and tightly) closed. WARNING: at this stage a quite important heat evolution along with pressure build up takes places in a matter of one minute, real care should be taken in choosing (and closing) the plastic bottle used. Operating under a well-ventilated hood should be one of the safety step taken. For our part, former 2.5 L ethanol bottles (with thus a large empty volume) sold by Merck-Prolabo (article 20 820 327) with a thickness of about 2 mm underwent some shape change but never ruptured when using the amount of reagents described above. Chemists who would choose to reproduce this work should either use proper quick-closing (or featuring the means to add a reagent under pressure) plastic-coated reactors, that we lacked, or take due precautions to avoid injury and poisoning in case of a bottle 'eruption'. This bottle (which was never reused) was left to cool overnight and cautiously opened. Ethanol (500 mL) was then added followed, portion-wise, by sodium methanolate (4.3 g, 0.08 mol). The resulting dark slurry was shaken and stirred until no more solid remained attached to the bottom of the bottle. The suspension was concentrated to dryness and after its adsorption on a portion of silica, the residue was purified by chromatography over silica gel eluting first with a 1:1 mixture of ethyl acetate–cyclohexane followed by ethyl acetate and then ethyl acetate containing 2% of triethylamine. The first fraction yielded variable amounts of unreacted benzonitrile and little unreacted safrole, the second fraction gave compound **9a**. This fraction was recrystallized, with some loss, in a mixture of ethanol and water to give compound **9a** (1.81 g, 17.2%). Mp=142 °C. ^{1}H NMR ($CDCl_3$): δ=1.42 (d, 3H, J=6.6 Hz), 2.49 (dd, 1H, J=13.2, 15.4 Hz), 2.68 (dd, 1H, J=5.2, 13.2 Hz), 3.60 (m, 1H), 3.85 (s, 9H), 5.94 (s, 2H), 6.70 (s, 1H), 6.74 (s, 3H). ^{13}C NMR ($CDCl_3$): δ=21.7, 33.8, 52.8, 56.2, 60.8, 101.2, 106.0, 108.0, 108.4, 122.6, 134.1, 138.8, 138.9, 145.9, 149.0, 153.1, 165.3. HRMS calcd for $C_{20}H_{22}NO_5$: 356.1498; found ($M+H^+$): 356.1495.

2.1.4. 6,7-Dimethoxy-3-methyl-1-(3,4,5-trimethoxyphenyl)-3,4-dihydroisoquinoline (9b). Following the above procedure, using 1 equiv. of methyleugenol and 3,4,5-trimethoxybenzonitrile as well as 1.1 equiv. of 54% tetrafluoroboric acid in ether, compound **9b** was obtained in 36% yield. Mp=140 °C (ethanol–water). ^{1}H NMR

($CDCl_3$): δ=1.42 (d, 3H, J=6.5 Hz), 2.50 (dd, 1H, J=13.5, 14.6 Hz), 2.70 (dd, 1H, J=5.2, 3.5 Hz), 3.61 (m, 1H), 3.71 (s, 3H), 3.89 (s, 6H), 3.84 (s, 3H), 3.91 (s, 3H), 6.73 (s, 1H), 6.79 (s, 2H), 6.80 (s, 1H). ^{13}C NMR ($CDCl_3$): δ=21.7, 32.2, 52.8, 56.0, 56.1, 60.8, 106.1, 110.4, 111.4, 121.2, 132.4, 134.6, 138.9, 146.9, 150.9, 152.9, 165.4. HRMS calcd for $C_{21}H_{25}NO_5$: 372.1811; found ($M+H^+$): 372.1802.

2.1.5. 7-Methyl-5-phenyl-7,8-dihydro-[1,3]dioxolo[4,5-*g*]isoquinoline (9c). From 1 equiv. of benzonitrile, 2 equiv. of safrole and 2 equiv. of 54% tetrafluoroboric acid in ether, following the same procedure described for **9a**, a 16% yield of compound **9c** was obtained. In this case, the waxy chromatographic fraction obtained was re-dissolved in dichloromethane, washed with a 1 N sodium hydroxide solution, water and then dried over magnesium sulfate before concentrating to dryness. ^{1}H NMR ($CDCl_3$): δ=1.41 (d, 3H, J=7.0 Hz), 2.50 (dd, 1H, J=12.8, 15.4 Hz), 2.72 (dd, 1H, J=5.2, 15.4 Hz), 3.63 (m, 1H), 5.94 (s, 2H), 6.68 (s, 1H), 6.71 (s, 1H), 7.40 (m, 3H), 7.51 (m, 2H). ^{13}C NMR ($CDCl_3$): δ=21.6, 33.8, 52.8, 101.2, 108.0, 108.5, 122.7, 128.1, 128.8, 129.1, 133.9, 138.3, 145.8, 149.9, 165.6. HRMS calcd for $C_{17}H_{15}NO_2$: 266.1181; found ($M+H^+$): 266.1184.

2.1.6. 7-Methyl-5-(3,4,5-trimethoxyphenyl)-[1,3]-dioxolo[4,5-*g*]isoquinoline (10). Compound **9a** (1.75 g, 4.9 mmol) and 10% palladium over charcoal (0.25 g, 0.246 mmol) were heated to reflux in decaline (80 mL) for 12 h. The suspension was diluted in dichloromethane, filtered and concentrated to dryness under vacuum. The residue was purified by chromatography over silica gel eluting with a 2:3 mixture of ethyl acetate–cyclohexane to give compound **10** (1.26 g, 72%). A small portion was recrystallized in aqueous methanol. Mp=149 °C lit.[19] 152–154 °C. ^{1}H NMR ($CDCl_3$): δ=2.65 (s, 3H), 3.87 (s, 6H), 3.88 (s, 3H), 6.04 (s, 2H), 6.79 (s, 2H), 7.02 (s, 1H), 7.25 (s, 1H), 7.31 (s, 1H). ^{13}C NMR ($CDCl_3$): δ=24.1, 56.2, 60.9, 101.5, 102.2, 103.2, 106.8, 118.0, 121.8, 135.7, 136.0, 138.2, 147.7, 149.9, 150.6, 153.2, 158.3. HRMS calcd for $C_{20}H_{20}NO_5$: 354.1341; found ($M+H^+$): 354.1339.

2.1.7. 7-Methyl-5-(3,4,5-trimethoxyphenyl)-[1,3]-dioxolo[4,5-*g*]isoquinoline *N*-oxide (11). Compound **10** (1.04 g, 2.9 mmol) was dissolved in dichloromethane (100 mL) and 70% 3-chloroperoxybenzoic acid (2.18 g, 8.8 mmol) was added. The solution was stirred overnight, further diluted in dichloromethane and washed with 1 N sodium hydroxide, water and then dried over magnesium sulfate to give compound **11** (0.98 g, 90%) pure enough for the next step. Mp=258 °C. ^{1}H NMR ($CDCl_3$): δ=2.62 (s, 3H), 3.84 (s, 6H), 3.92 (s, 3H), 6.03 (s, 2H), 6.62 (s, 2H), 6.66 (s, 1H), 6.99 (s, 1H), 7.48 (s,1H). ^{13}C NMR ($CDCl_3$): δ=18.0, 56.0, 60.8, 101.6, 101.7, 102.2, 106.8, 121.5, 125.7, 126.8, 127.6, 138.2, 144.3, 145.4, 149.0, 149.3, 153.6. HRMS calcd for $C_{20}H_{20}NO_6$: 370.1291; found ($M+H^+$): 370.1290.

2.1.8. 5-(3,4,5-Trimethoxyphenyl)-[1,3]dioxolo[4,5-*g*]isoquinolin-7-yl]-methanol (12). Compound **11** (0.65 g, 1.76 mmol) and acetic anhydride (2 mL, 21.2 mmol) were refluxed in 1,2-dichlorobenzene (60 ml) for 4 h. The solution was concentrated to dryness and the residue was stirred in 70% aqueous ethanol (80 mL) containing sodium hydroxide (0.8 g, 0.02 mol) at 50 °C for 30 min. The resulting solution was made acid with 1 N hydrochloric acid, saturated with sodium chloride and extracted with dichloromethane. The organic layer was washed with brine and dried over magnesium sulfate before concentrating to dryness. The residue was recrystallized in toluene to give compound **12** (0.4 g, 61%). Mp=161 °C. ^{1}H NMR ($CDCl_3$): δ=3.90 (s, 6H), 3.93 (s, 3H), 4.88 (s, 2H), 6.09 (s, 2H), 6.83 (s, 2H), 7.11 (s, 1H), 7.34 (s, 1H), 7.48 (s,1H). ^{13}C NMR ($CDCl_3$): δ=56.2, 60.9, 64.7, 101.7, 102.7, 103.3, 106.8, 115.9, 123.1, 135.2, 136.0, 138.3, 148.3, 150.9, 150.95, 153.2, 158.1. HRMS calcd for $C_{20}H_{20}NO_6$: 370.1291 found ($M+H^+$): 370.1288.

2.1.9. 5-(3,4,5-Trimethoxyphenyl)-[1,3]dioxolo[4,5-*g*]isoquinoline-7-carbaldehyde (13). Compound **12** (0.35 g, 0.95 mmol) and Dess–Martin periodinane[26] (0.6 g, 1.42 mmol) were stirred in dichloromethane (50 mL) for 2 h. The solution was diluted with more dichloromethane and washed with 1 N sodium hydroxide, water and dried over magnesium sulfate before concentrating to dryness to give aldehyde **13** (0.32 g, 91%) which could be used directly for the next step or recrystallized in aqueous ethanol. Mp=145–146 °C. ^{1}H NMR ($CDCl_3$): δ=3.88 (s, 6H), 3.90 (s, 3H), 6.13 (s, 2H), 6.83 (s, 2H), 7.26 (s, 1H), 7.38 (s, 1H), 8.17 (s,1H), 10.20 (s, 2H). ^{13}C NMR ($CDCl_3$): δ=56.2, 60.9, 102.2, 103.8, 104.6, 106.8, 119.3, 126.8, 134.5, 134.8, 138.6, 145.4, 150.7, 151.2, 153.3, 159.2, 193.8. HRMS calcd for $C_{20}H_{18}NO_6$: 368.1134; found ($M+H^+$): 368.1127.

2.1.10. 5-(3,4,5-Trimethoxyphenyl)-[1,3]dioxolo[4,5-*g*]isoquinoline-7-carboxylic acid (2). Compound **13** (0.32 g, 0.87 mmol) was dissolved in acetonitrile (30 mL), water (5 mL) and silver nitrate (0.7 g, 4.12 mmol) were added to the solution followed by sodium hydroxide (0.26 g, 6.5 mmol). The blackening solution was stirred for 90 min and made acid with 1 N hydrochloric acid. This was saturated with sodium chloride and extracted with dichloromethane. The organic layer was washed with brine and dried over magnesium sulfate before concentrating to dryness. The residue was recrystallized in a mixture of toluene and heptane to give acid **2** (0.24 g, 71%). Mp=229 °C. ^{1}H NMR ($CDCl_3$): δ=3.90 (s, 6H), 3.95 (s, 3H), 6.16 (s, 2H), 6.81 (s, 2H), 7.30 (s, 1H), 7.44 (s, 1H), 8.45 (s,1H). ^{13}C NMR ($CDCl_3$): δ=54.4, 61.0, 102.4, 104.0, 104.4, 106.9, 121.0, 126.4, 133.7, 135.9, 137.8, 138.9, 150.8, 151.7, 153.4, 157.5, 165.1. HRMS calcd for $C_{20}H_{18}NO_7$: 384.1083; found ($M+H^+$): 384.1090.

References and notes

1. Janin, Y. L.; Roulland, E.; Beurdeley-Thomas, A.; Decaudin, D.; Monneret, C.; Poupon, M.-F. *J. Chem. Soc. Perkin Trans. I* **2002**, 529–532.
2. Decaudin, D.; Castedo, M.; Nemati, F.; Beurdeley-Thomas, A.; De Pinieux, G.; Caron, A.; Pouillart, P.; Wijdenes, J.; Rouillard, D.; Kroemer, G.; Poupon, M. F. *Cancer Res.* **2002**, *62*, 1388–1393.
3. Casellas, P.; Galiegue, S.; Basile, A. S. *Neurochemistry Int.* **2002**, *40*, 475–486.

4. Beurdeley-Thomas, A.; Miccoli, L.; Oudard, S.; Dutrillaux, B.; Poupon, M.-F. *J. Neuro-Oncol.* **2000**, *46*, 45–56.
5. Batra, S.; Sabnis, Y. A.; Rosenthal, P. J.; Avery, M. A. *Bioorg. Med. Chem.* **2003**, *11*, 2293–2299.
6. Capilla, A. S.; Romero, M.; Pujol, M. D.; Caignard, D. H.; Renard, P. *Tetrahedron* **2001**, *57*, 8297–8303.
7. Capilla, A. S.; Sanchez, I.; Caignard, D. H.; Renard, P.; Pujol, M. D. *Eur. J. Med. Chem.* **2001**, *36*, 389–393.
8. Bermejo, A.; Andreu, I.; Suvire, F.; Léonce, S.; Caignard, D. H.; Renard, P.; Pierré, A.; Enriz, R. D.; Cortes, D.; Cabedo, N. *J. Med. Chem.* **2002**, *45*, 5058–5068.
9. Janin, Y. L.; Zoltobroda, G.; Huel, C.; Monneret, C. *J. Carbohydrate Chem.* **2002**, *21*, 275–286.
10. Hickey, D. M. B.; MacKenzie, A. R.; Moody, C. J.; Rees, C. W. *J. Chem. Soc. Perkin Trans. I* **1987**, 921–927.
11. Gautier, N.; Dodd, R. H. *Synth. Commun.* **1998**, *28*, 3769–3777, and references cited therein.
12. Tucker, S. C.; Brown, J. M.; Oakes, J.; Thornthwaite, D. *Tetrahedron* **2001**, *57*, 2545–2554.
13. Hiebl, J.; Kollmann, H.; Levinson, S. H.; Offen, P.; Shetzline, S. B.; Badlani, R. *Tetrahedron Lett.* **1999**, *40*, 7935–7943.
14. Stiller, E. T. *J. Chem. Soc.* **1937**, 473–476.
15. Chattopadhyay, S. K.; Maity, S.; Pal, B. K.; Panja, S. *Tetrahedron Lett.* **2002**, *43*, 5079–5081.
16. Fodor, G.; Nagubandi, S. *Tetrahedron* **1980**, *36*, 1279–1300.
17. Whaley, W. M.; Govindachari, T. R. *Org. React.* **1951**, *6*, 74–150.
18. Whaley, W. M.; Govindachari, T. R. *Org. React.* **1951**, *6*, 151–190.
19. Bruckner, V.; von Fodor, G. *Ber. Chem.* **1938**, *71*, 541–549.
20. Krimen, L. I.; Cota, D. J. *Org. React.* **1969**, *17*, 213–325.
21. Ho, T.-L.; Chein, R.-J. *J. Org. Chem.* **2004**, *69*, 591–592.
22. Ritter, J. J.; Murphy, F. X. *J. Am. Chem. Soc.* **1952**, *74*, 763–765.
23. Kametani, T.; Kano, S. *J. Pharm. Soc. Jpn* **1952**, *72*, 1539–1541, *Chem. Abstr.* **1953**, 10538.
24. Madroñero, R.; Alvarez, E. F.; Lora-Tamayo, M. *An. Quim.* **1955**, *51B*, 465–468, *Chem. Abstr.* **1956**, 7805e.
25. Madroñero, R.; Fernàndez, E. A.; Lora-Tamayo, M. *An. Quim.* **1955**, *51B*, 276–282, *Chem. Abstr.* **1956**, 3445b.
26. Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287.